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14. ABSTRACT

The objective of this research is to further our understanding of the molecular mechanisms underlying the aggressive growth of estrogen receptor (ER)-negative, basal-like breast tumors. My goal is to determine if SKP2 is a viable new therapeutic target to specifically treat patients who have tumors that are independent of ER signaling. The most significant result was determining that knockdown of SKP2 in TMX2-28 cells shifted the cell cycle resulting in a significant increase in the percentage of cells in the G1/G0 phase, as well as a significant decrease in the percentage of cells in the S-phase of the cell cycle.

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ER-negative, Breast Cancer, SKP2

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Introduction:

The objective of this research is to further our understanding of the cellular and molecular mechanisms underlying the aggressive growth of ER-negative, basal-like tumors. The goal is to identify new therapeutic targets to specifically treat patients that have tumors that are independent of ER signaling as these tumors are more often ER-negative. Past work from our lab and others has suggested that S-phase kinase-associated protein 2 (SKP2) plays an important role in breast tumorigenesis and would make a good therapeutic target. By utilizing three models (human tissue, animal models, and tissue culture) in which to characterize the role of SKP2 in breast cancer, we can obtain a better understanding of the molecular mechanisms underlying the aggressive tumor growth of basal-like breast tumors. It is anticipated that results from these studies will show that SKP2 would make a good therapeutic target for the treatment of women with basal-like tumors that are often associated with poor clinical outcome and tend to be ER-negative.

Body:

Task 1: During the third year of this study, I studied alteration in cell cycle when SKP2 is knockdown in TMX2-28 cells. It was determined that knockdown of SKP2 in TMX2-28 cells shifted the cell cycle resulting in a significant increase in the percentage of cells in the G1/G0 phase, as well as a significant decrease in the percentage of cells in the S-phase of the cell cycle.

Task 2: I have continued to collaborate with Dr. Otis at Baystate Medical Center in order to collect tissue, and assess protein expression of SKP2 and its associated proteins on the pathological level.

Task 3: *In vivo* studies are currently ongoing to determine growth and metastasis patterns *in vivo.*

Key Research Accomplishments:

Training Accomplishments:

- Continue collaborations with **Dr. Christopher Otis**, Director of Surgical Pathology at Baystate Medical Center; **Dr. Brian Pentecost**, New York Department of Health,; **Dr. Sallie Smith-Schneider**, Pioneer Valley Life Sciences Institute; and **Dr. Douglas Anderton**, Associate Dean for Research Affairs, Director of Social and Demographic Research Institute
- Current and active member of AACR, AAAS, and SACNAS
- Continue to talk and meet with my mentor Dr. Kathleen Arcaro on a daily basis
- Attend weekly cancer and chemoprevention journal club, apoptosis journal club, molecular and cellular biology seminar and colloquia, animal biotechnology and biomedical science seminar

Research accomplishments:

- Determined alteration in cell cycle effects resulting from SKP2 knockdown in TMX2-28 cells
- Continued pathological studies of SKP2 pathway proteins in human breast cancer samples
- Began *in vivo* studies on growth and metastasis using TMX2-28 cells as well as SKP2 knockdown TMX2-28 cells

Reportable Outcomes:

Over the past three years, my data suggest that overexpression of SKP2 and the subsequent dysregulation of the cell cycle plays a role in the development of the highly proliferative and aggressive nature of triple-negative and basal-like breast cancers.

Conclusion:

The third year of this study has led to the completion of cell cycle analysis studies, initiation of *in vivo* studies, and the continuation of my training through collaborations and interactions with a number of clinicians, pathologists, bench scientists and epidemiologists. In the final year of this study I expect to complete all remaining immunohistochemical, protein expression, and *in vivo* work.

References: None

Appendices: None